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SCHEIN
PHARMACEUTICAL

October 26, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Comments On Proposed Regulations For 180-Day Generic Drug Exclusivity For Abbreviated New Drug Applications As Published In The Federal Register, Vol. 64, No. 151, August 6, 1999

Dear Sir or Madam:

This letter comprises the comments of Schein Pharmaceutical, Inc. ("Schein") to the FDA's proposed regulations for 180-day generic drug exclusivity for abbreviated new drug applications as published in the Federal Register, Vol. 64, No. 151, August 6, 1999. As requested, two copies of this communication are enclosed.

INTRODUCTION

A key provision of the proposed regulations is a 180-day triggering period and the concomitant requirement that a triggering event occur within the 180-day triggering period in the absence of which the first paragraph IV filer will lose its eligibility for 180-day exclusivity. It is likely that this aspect of the proposed regulation will be challenged as beyond FDA's regulatory authority, just as other aspects of FDA's exclusivity regulations have been challenged, e.g., the "successful defense" requirement.

Schein agrees, however, that a triggering mechanism which forces the first paragraph IV filer to "use it or lose it" is a viable mechanism for promoting the statutory goals of fostering generic competition at the earliest possible time.

While the over all regulatory scheme proposed by FDA is constructive, Schein believes that specific aspects of the proposed regulations requires some fine-tuning. Schein's specific comments concerning the proposed regulations are set forth below.

1. A Declaratory Judgment Action By The First Applicant Should Delay The Triggering Period

Proposed § 314.107(c)(5)(i) provides for delay of the triggering period for up to 30 months in circumstances where the first paragraph IV filer has been sued by the patent owner or NDA holder. However, there is no corresponding delay of the triggering period where the first applicant initiates a declaratory judgment action seeking a determination that a listed patent is not infringed, invalid or unenforceable.

As FDA undoubtedly appreciates, a prudent first applicant may want a litigated resolution before launching a generic product. Nor does Schein perceive any logical reason why declaratory judgment actions should be treated differently from affirmative suits by patent owners or NDA holders with respect to delay of the triggering period. Accordingly, subject to other events which impact the start of the triggering period (e.g., preliminary injunction), the regulations should provide that the triggering period is delayed by a declaratory judgment action filed before the triggering period starts, and that such delay does not extend beyond 30 months from the date the patent owner or NDA holder received notice of the patent certification from the first filer.

2. Final Court Decision By Subsequent ANDA Applicant Should Start First Applicant's Exclusivity Period Even If A Trigger Period Is Running

Proposed § 314.107(c)(5)(i) provides that a first applicant "will" receive exclusivity if any of the circumstances enumerated in (A)-(E) apply. Each of (A)-(E) provides that an eligible applicant will receive exclusivity if, during the 180-day trigger period a "triggering event" occurs. Proposed § 314.107(a)(2) defines a "triggering event" as occurring when "during a triggering period, a first applicant commercially markets its drug product or obtains a favorable court decision", i.e., a favorable court decision is a triggering event only if it occurs in the first applicant's court action. So, as worded, proposed § 314.107(c)(5)(i)(A)-(E) could

be interpreted as guaranteeing an eligible applicant 180 days of exclusivity provided the first applicant either commercially markets or obtains a favorable court decision during a triggering period.

Such an interpretation, however, would be inconsistent with the statutory scheme which provides that an eligible applicant's exclusivity period begins to run from the date of a final court decision in *any* court action, i.e., a court action involving the first or any subsequent ANDA applicant. Therefore, to avoid misinterpretation of the proposed regulation, it should be clarified that even under the circumstances enumerated in proposed § 314.107(c)(5)(i)(A)-(E), an eligible applicant's 180-day exclusivity period will begin to run immediately in the event of *any* final court decision holding the relevant patents invalid, unenforceable or not infringed, even if such final court decision occurs during a triggering period.

3. The Reference To "Only Obstacle" In Proposed § 314.107(c)(5)(i) Should Be Clarified

Proposed § 314.107(c)(5)(i) provides that, in the circumstances enumerated in (A)-(E), a triggering period will begin to run if a subsequent applicant receives a tentative approval for its drug product stating that the first applicant's eligibility for 180-day exclusivity is the "only

obstacle" to final approval of the subsequent ANDA. Schein believes it would be helpful if the obstacles contemplated by the proposed regulation were clarified. In this regard, Schein believes that all the following constitute obstacles to approval of a subsequent applicant which should preclude the running of a triggering period: any patent which blocks the subsequent applicant from marketing and for which the subsequent applicant has filed a paragraph III certification; any new chemical entity, new use or data exclusivity in favor of the innovator which blocks the subsequent applicant from marketing; pediatric exclusivity which blocks the subsequent applicant from marketing; where the subsequent applicant has filed a paragraph IV certification and is subject to a 30 month stay of approval or a preliminary injunction which blocks the subsequent applicant from marketing.

4. If A First Applicant Has Submitted Paragraph IV Certifications To Multiple Patents, A Final Court Decision On Less Than All Of Those Patents Should *Not* Trigger The Running Of The First Applicant's Exclusivity

Although not explicit in the proposed regulations, FDA's commentary explains that if an applicant eligible for exclusivity has submitted paragraph IV certifications to multiple patents, the first court decision finding any one of the patents invalid, unenforceable or not infringed will trigger the running of the eligible applicant's exclusivity. See Federal Register at 42876 (unless otherwise noted, all references to the Federal Register are to Vol. 64, No. 151, August 6, 1999). Schein believes that it is unfair to deny an eligible applicant exclusivity under these

circumstances. Oftentimes, to obtain the earliest possible market entry, a first applicant must challenge multiple listed patents. It would be contrary to the policy of the Hatch-Waxman Act to deny such an applicant exclusivity, as it would reduce the first applicant's incentive to seek the earliest possible market entry by challenging multiple patents. Nor does Schein perceive any other reason why FDA's position should not be modified to specify that where an eligible applicant challenges multiple listed patents, final court decisions on *all* multiple listed patents are required to trigger the running of the eligible applicant's exclusivity. FDA's adoption of a triggering period insures that the first applicant's litigation will not unduly delay generic competition.

5. A 180-Day Triggering Period Is Too Long; 60 Days Is More Appropriate

FDA's rationale for the 180-day duration of the triggering period is loosely premised on the statute, which contemplates the possibility of no generic competition during the 180-day exclusivity period. See Federal Register at 42878. However, as FDA acknowledges, when the triggering period and exclusivity periods are combined, which FDA characterizes as an "extreme" case, there is the possibility that generic competition will be delayed for up to 360 days.

Considering the statutory goal of insuring generic competition at the earliest possible time while providing an incentive in the form of exclusivity to the first applicant to challenge a listed patent, it would be more appropriate to shorten the triggering period to 60 days. A shorter triggering period would accelerate the entry of generic products regardless of whether such entry results from accelerated entry by the first applicant, lapse of the first applicant's exclusivity period or waiver of the first applicant's exclusivity in favor of a subsequent applicant. Nor does Schein perceive any inequity to the first applicant from a shortened trigger period.

While the FDA has contemplated a 60-day triggering period in specific cases (see Federal Register notice at 42878), Schein believes that a 60-day triggering period is appropriate in all cases. Of course, Schein also agrees with the more limited application of a 60-day triggering period as proposed by FDA in the Federal Register.

6. Desirability of Rolling Exclusivity

FDA's proposed regulations do not contemplate rolling exclusivity, i.e., awarding exclusivity to a subsequent paragraph IV filer when the first applicant becomes ineligible. Irrespective of FDA's adoption of a triggering period, Schein supports a rolling exclusivity because it

provides a further incentive for subsequent applicants to file and diligently prosecute ANDAs with paragraph IV certifications, and because it minimizes the possibility of collusion between the first filer and the NDA holder or patent owner.

The commentary to the proposed regulations explains FDA's rationale for rejecting rolling exclusivity, but also invites comments on the issue. As noted in FDA's commentary, the statutory language would support a rolling exclusivity in which the next-in-line applicant becomes eligible for exclusivity once the first applicant becomes ineligible. FDA should consider that an effect of the proposed regulations will be an increased likelihood that NDA holders and patent owners will pursue litigation against all applicants filing ANDAs with paragraph IV certifications, as the proposed regulations prevent an NDA holder or patent owner from blocking marketing approvals for subsequent applicants by reaching an agreement with the first filer. As FDA knows, patent litigation is an expensive proposition and, typically, is a far greater financial burden on the generic company than the NDA holder or patent owner which, more often than not, is a Fortune 500 Company. Therefore, to promote the statutory scheme it is desirable to provide as much incentive as possible to *all* ANDA applicants, and this goal is fostered by rolling exclusivity.

Schein does not perceive any regulatory difficulties in implementing a "next-in-line" rolling exclusivity, nor does FDA cite any such difficulties. It would seem feasible that once the first

filer becomes ineligible, the next-in-line ANDA applicant with a paragraph IV certification could be treated, for all purposes, as a first filer and subject to all of the regulations affecting a first filer's eligibility for exclusivity.

7. Requirement For A "Substantially Complete" ANDA.

Under FDA's regulations, the first applicant's ANDA must be "substantially complete" at the time of filing for the first applicant to qualify for 180-day exclusivity. See definition of *first applicant* in proposed § 314.107(a)(2). Although not evident from FDA's proposed definition of *substantially complete* in § 314.107(a)(2), the commentary to the proposed regulations explains that a first applicant will lose eligibility for exclusivity if it is required to conduct a new bioequivalence study to obtain ANDA approval. See Federal Register at 42875. FDA's rationale is its concern that the eligibility for exclusivity attaching to the first paragraph IV filer will encourage applicants to file shoddy bioequivalence studies.

While the FDA's rationale is sound, the solution is harsh, as there are situations where a new bioequivalence study may be required for reasons beyond the applicant's control. This may happen, for example, where a new study is required by a change in FDA's position or because

a bulk supplier (i.e., DMF holder) advises the applicant that the drug substance used in the biostudy is no longer available to the applicant.

Accordingly, it is suggested that FDA modify its position as expressed in the proposed regulations by providing that the first paragraph IV filer will be eligible for exclusivity as long as its ANDA is "accepted for filing", irrespective of whether its bioequivalence study is subsequently rejected. If FDA does not adopt "accepted for filing" language, then it is alternatively requested that FDA clarify that an ANDA will be considered "substantially complete" if a new bioequivalence study is required for reasons beyond the applicant's control.

Schein recognizes, of course, that the regulatory review period will be lengthened when an ANDA applicant is required to execute a new bioequivalence study. However, the "triggering period" provisions of the proposed regulations insure that the first filer's eligibility for exclusivity will not indefinitely bar subsequent applicants from marketing approval. Consequently, the modification proposed by Schein does not disrupt the statutory goal of insuring early entry of generic competition.

8. A Change From A Paragraph IV Certification To A Paragraph III Certification Should Only Be Required After A *Final* Court Decision

As presently worded, proposed § 314.107(c)(3) requires the first paragraph IV filer to amend its paragraph IV certification to a paragraph III certification after a "court decision" finding a relevant patent infringed. The term "court decision" is not specifically defined, and as worded the cited provision could be construed to require a change in certification following a district court decision. Of course, however, there is the possibility that an unfavorable district court decision could be reversed on appeal, and there is no reason why an otherwise eligible applicant should be denied exclusivity solely because it obtains an unfavorable decision at the district court level. It is suggested, therefore, that proposed § 314.107(c)(3) be modified to clarify that a change in certification is only required after a *final* court decision finding the patent infringed.

9. There Should Be Only One 30 Month Period

The proposed regulations should clarify that for each drug product there is only one 30 month period per ANDA. For example, if an NDA holder lists a new patent after an ANDA applicant has forwarded a notice of patent certification for a previously listed patent, the 30 month delay of approval arising from a law suit based on the previously listed patent should

not be extended by litigation arising from a patent certification with respect to the later listed patent. Accordingly, it should be clarified that once the 30 month delay of approval begins to run with respect to a paragraph IV filer, there should be no further 30 month approval delays arising from litigation of other listed patents.

10. Waiver Of Exclusivity Should Be Permitted Before The Exclusivity Period Starts

Schein supports an eligible applicant's right to waive exclusivity in favor of a subsequent applicant. However, proposed § 314.107(e) provides that an eligible applicant can waive exclusivity in favor of one or more subsequent applicants only *after* the 180-day exclusivity has started. Schein perceives no logical reason why an eligible applicant should not be permitted to waive its entitlement to exclusivity *before* the 180-day exclusivity period begins. Indeed, sound commercial consideration suggests that an eligible applicant should be permitted to waive its entitlement to exclusivity at any time.

As proposed, the eligible applicant would have to give notice of the proposed waiver during the exclusivity period, whereupon the FDA would review it and, if accepted, provide notice of approval to the affected subsequent applicant(s). Inevitably, this will result in a *de facto* reduction of the 180-day exclusivity period, delay generic marketing and reduce the value of the exclusivity period.

Presumably FDA's rationale for the proposed regulation is that a waiver of exclusivity should not be effective until exclusivity has actually "vested" in the eligible applicant, as there are situations where an applicant may lose its eligibility for exclusivity. However, this can be addressed by providing that an eligible applicant's waiver of exclusivity only becomes effective once exclusivity vests in the eligible applicant, i.e., once the 180-day exclusivity period begins. This modification accomplishes FDA's objective without eating into the 180-day exclusivity period.

11. FDA Is Without Authority To List Patents Submitted More Than 30 Days After Issue

Although not incorporated in the proposed regulations, it is evident from the commentary (Federal Register at 42875) and from FDA's past practice that FDA will list in the Orange Book a patent submitted by the NDA holder more than 30 days after the patent issues. FDA's position in this regard is contrary to the statutory mandate. Accordingly, FDA should clarify that untimely filed patents will no longer be listed.

The statutory scheme established at 21 U.S.C. § 355 is clear and unambiguous. 21 U.S.C. § 355(b)(1) provides that an NDA applicant should submit patent information at the time of filing for any patent in effect as of the NDA filing date, or after filing and before approval with

respect to any patent issuing after filing but before approval. 21 U.S.C. § 355(c)(2) addresses the situation where a patent issues after approval of the NDA. In that event, the statute provides:

> If the holder of an approved application could not file patent information under subsection (b) . . . because no patent had been issued when an application was filed or approved, the holder *shall* file such information under this subsection *not later than 30 days after the date the patent involved is issued.* (Emphasis added)

The statutory language is subject to only one interpretation. Where a patent issues after an NDA is filed or approved, the NDA holder *shall* file information concerning such patent not later than 30 days after the patent issues. There is nothing ambiguous about this language and there is no authority for FDA to accept patents which are filed outside the 30 day window. Nor does enforcement of this statutory provision require FDA to acquire expertise in arcane patent issues. All FDA need do is look at the issue date of the patent and then determine if the patent information was submitted within 30 days of its issue date, a purely administrative function.

Accordingly, FDA should clarify, for once and for all, that it will not accept patent information for listing in the Orange Book if such information is not submitted within the time frame afforded by the statute.

12. FDA Should Modify The Retroactive Effect Of The Proposed Regulation

In its proposed implementation plan (Federal Register at 42882) FDA proposes to apply any final rule to ANDAs pending as of the effective date of the rule and to subsequently submitted ANDAs. Schein believes that it is inappropriate to apply a final rule to ANDAs that are pending as of the effective date of the final rule, as it ignores the reality that ANDA applicants have made substantive decisions and substantial investments based on the current regulations, imperfect though they may be. It is inequitable to alter the rules of the game after such decisions have been made, and certainly where an ANDA applicant has filed an application before the effective date of the final rule.

Schein proposes, therefore, that any final rule based on the proposed regulations apply only to ANDAs accepted for filing after the effective date of the final rule.

13. The Reference To "Approval" In Proposed § 314.107(c)(5)(i)(A) And (B) Should Be Clarified

Proposed § 314.107(c)(5)(i)(A) refers to a first applicant who has "received *approval* for its drug product", and proposed § 314.107(c)(5)(i)(B) refers to a first applicant who "has not received *approval* for its drug product". Other sections of the proposed regulations refer to "tentative approval (see, e.g., § 314.107(c)(5)(i)) or to "full approval" (see, e.g., proposed § 314.107(c)(5)(i)(E)). While "tentative approval" and "full approval" are well understood terms, "approval" has no definite meaning and could be construed as either tentative approval or full approval. Schein believes from the context of the proposed regulation that "full approval" is intended in proposed § 314.107(c)(5)(i)(A) and (B). This should be clarified by substituting "full approval" for "approval" in these sections of the proposed regulations.

14. Proposed § 314.107(f)(2) Should Be Clarified

Proposed § 314.107(f)(2) requires submission to FDA of the entry of an order or judgment in a court action within 10 days of a final judgment. However, there is no guidance as to what happens if the submission does not occur within 10 days. This should be clarified.

Also, the regulation provides that the patent owner and NDA holder may also submit a copy of the entry of an order or judgment to FDA. It is suggested that the proposed regulation be modified by providing that if a patent owner or NDA holder submits such information, it must also provide a copy to the applicant at the same time.

15. Proposed § 314.107(h)(2) Should Be Clarified

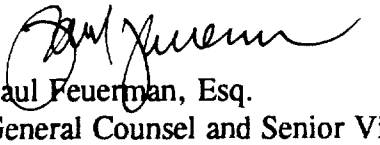
Proposed § 314.107(h)(2) requires an ANDA applicant or 505(b)(2) applicant to notify FDA "immediately" of any legal action filed against the applicant within the 45 day period following receipt of the notice of certification. However, this proposed regulation does not take into account that an action may be filed but not served on the applicant for up to 120 days or more. See Rule 4m of the Federal Rules of Civil Procedure. Therefore, it is possible that an action may be filed within 45 days of receipt of the notice of certification, but that the applicant will not be aware of it.

It is suggested, therefore, that FDA modify the proposed regulation by providing that the applicant's obligation to notify FDA in writing of the filing of any legal action should only attach once the applicant is served with the complaint in the action.

Proposed § 314.107(h)(2)(v) should also be clarified. This provision states that the patent owner and NDA holder may also notify FDA of the filing of a legal action for patent infringement. It is suggested that this proposed regulation be modified by providing that if the patent owner or NDA holder provides such notice to FDA, that it must also provide a copy of such notice to the applicant at the same time.

Should FDA have any questions concerning the foregoing comments, please contact the undersigned at 973-593-5960.

Very truly yours,



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